THYROID DISEASE AND AUTOIMMUNE THYROIDITIS

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Introduction

Hypothyroidism is the most common endocrine disorder of canines, and up to 80% of cases result from autoimmune (lymphocytic) thyroiditis. The heritable nature of this disorder poses significant genetic implications for breeding stock. Thus, accurate diagnosis of the early compensatory stages of canine autoimmune thyroiditis leading up to hypothyroidism affords important genetic and clinical options for prompt intervention and case management.

Although thyroid dysfunction is the most frequently recognized endocrine disorder of pet animals, it is often difficult to make a definitive diagnosis. As the thyroid gland regulates metabolism of all body cellular functions, reduced thyroid function can produce a wide range of clinical manifestations. Many of these clinical signs mimic those resulting from other causes and so recognition of the condition and interpretation of thyroid function tests can be problematic.

Baseline Thyroid Profiles

A complete baseline thyroid profile is measured and typically includes total T4, total T3, free T4, free T3, T3AA and T4AA, and can include cTSH and/or TgAA. The TgAA assay is especially important in screening breeding stock for heritable autoimmune thyroid disease.

The normal reference ranges for thyroid analytes of healthy adult animals tend to be similar for most breeds of companion animals. Exceptions are the sighthound and giant breeds of dogs which have lower basal levels. Typical thyroid levels for healthy sighthounds, such as retired racing greyhounds, are at or just below the established laboratory reference ranges, whereas healthy giant breeds have optimal levels around the midpoint of these ranges.

Similarly, because young animals are still growing and adolescents are maturing, optimal thyroid levels are expected to be in the upper half of the references ranges. For geriatric animals, basal metabolism is usually slowing down, and so optimal thyroid levels are likely to be closer to midrange or even slightly lower.

Genetic Screening for Thyroid Disease

Most cases of thyroiditis have elevated serum TgAA levels, whereas only about 20-40% of cases have elevated circulating T3 and/or T4 AA. Thus, the presence of elevated T3 and/or T4 AA confirms a diagnosis of autoimmune thyroiditis but underestimates its prevalence, as negative (non-elevated) autoantibody levels do not rule out thyroiditis. Measuring TgAA levels also permits early recognition of the disorder, and facilitates genetic counselling. Affected dogs should not be used for breeding.

The commercial TgAA test can give false negative results if the dog has received thyroid supplement within the previous 90 days, thereby allowing unscrupulous owners to test dogs while on treatment to assert there normalcy, or to obtain certification with health registries such as the OFA Thyroid Registry. False negative TgAA results also can occur in about 5% of dogs

verified to have high T3AA and/or T4AA. Furthermore, false positive TgAA results may be obtained if the dog has been vaccinated within the previous 30-45 days, or in some cases of non-thyroidal illness. Vaccination of pet and research dogs with polyvalent vaccines containing rabies virus or rabies vaccine alone was recently shown to induce production of antithyroglobulin autoantibodies, a provocative and important finding with implications for the subsequent development of hypothyroidism

A population study of 287,948 dogs was recently published by the MSU Animal Health Diagnostic Laboratory. Circulating thyroid hormone autoantibodies (T3AA and/or T4AA)) were found in 18,135 of these dogs (6.3%). The 10 breeds with the highest prevalence of thyroid AA from their study were: Pointer, English Setter, English Pointer, Skye Terrier, German Wirehaired Pointer, Old English Sheepdog, Boxer, Maltese, Kuvasz, and Petit Basset Griffon Vendeen. Prevalence was associated with body weight and was highest in dogs 2-4 years old. Females were significantly more likely to have thyroid AA than males.

A bitch with circulating thyroid AA has the potential to pass these along to the puppies transplacentally as well as via the colostrum. Furthermore, any dog having thyroid AA may eventually develop clinical symptoms of thyroid disease and/or be susceptible to other autoimmune diseases. Thyroid screening is thus very important for selecting potential breeding stock as well as for clinical diagnosis.

Thyroid testing for genetic screening purposes is less likely to be meaningful before puberty. Screening is initiated, therefore, once healthy dogs and bitches have reached sexual maturity (between 10-14 months in males and during the first anestrous period for females following their maiden heat). As the female sexual cycle is quiescent during anestrus, any influence of sex hormones on baseline thyroid function will be minimized. This period generally begins 12 weeks from the onset of the previous heat and lasts one month or longer. The interpretation of results from baseline thyroid profiles in intact females will be more reliable when they are tested in anestrus. In fact, genetic screening of intact females for other disorders such as von Willebrand disease (vWD), hip dysplasia, and wellness or reproductive checkups (vaginal cultures, hormone testing) is best scheduled during anestrus. Once the initial thyroid profile is obtained, dogs and bitches should be rechecked on an annual basis to assess their thyroid function and overall health. Generation of annual test results provides comparisons that permit early recognition of developing thyroid dysfunction. This allows for early treatment, where indicated, to avoid the appearance or advancement of clinical signs associated with hypothyroidism.

Canine autoimuune thyroid disease is very similar to Hashimoto's thyroiditis of humans, which has been shown to be associated with human major histocompatibility complex (MHC) tissue types. A similar association with canine MHC genes in hypothyroid dogs has recently been reported in Doberman Pinschers, English Setters and Rhodesian Ridgebacks, who share a rare dog leukocyte antigen (DLA) class II haplotype which contains a unique DLA-DQA1*00101 genetic determinant. While the presence of this determinant doubles the risk of a dog developing hypothyroidism, it was not found in boxers affected with thyroiditis, nor was it found in the Shih Tzu, Yorkshire Terrier, or Siberian Husky, although more studies are needed in these and other susceptible breeds to establish their true status with respect to this marker DLA antigen. This exciting finding of a common genetic determinant associated with thyroid disease in several breeds hopefully will lead to development of a genetic marker test to identify affected breeding stock and allow for selective breeding to reduce disease incidence in pure-bred dogs.

Polyglandular Autoimmunity

Individuals genetically susceptible to autoimmune thyroid disease may also become more susceptible to immune-mediated diseases affecting other target tissues and organs, especially the bone marrow, liver, adrenal gland, pancreas, skin, kidney, joints, bowel, and central nervous system. The resulting "polyglandular autoimmune syndrome" of humans is becoming more commonly recognized in the dog, and probably occurs in other species as well. The syndrome tends to run in families and is believed to have an inherited basis. Multiple endocrine glands and nonendocrine systems become involved in a systemic immune-mediated process. This multiple endocrinopathy often occurs in patients with underlying autoimmune thyroid disease (hypo- or hyperthyroidism) and concurrent Addison's disease, diabetes, reproductive gonadal failure, skin disease and alopecia, and malabsorption syndrome. The most common nonendocrinologic autoimmune disorders associated with this syndrome are autoimmune hemolytic anemia (AIHA), idiopathic thrombocytopenic purpura (ITP), chronic active hepatitis, and immune-complex glomerulonephritis (systemic lupus erythematosus; SLE).

The most commonly recognized polyglandular endocrinopathy of dogs is Schmidt's syndrome (thyroiditis and Addison's disease). Examples of breeds genetically predisposed to this disorder include the Standard Poodle, Old English Sheepdog, Bearded Collie, Portuguese Water Dog, Nova Scotia Duck Tolling Retriever, and Leonberger, although any breed or mixed breed can be affected. Our study cohort of 162 cases of autoimmune blood and endocrine disorders in Old English Sheepdogs (1980-1989) included 115 AIHA and/or ITP, 99 thyroid disease, 23 Addison's disease, 7 vaccine reactions, 3 SLE, 2 diabetes, 1 rheumatoid arthritis and 1 hypoparathyroidism. The group comprised 110 females (15 spayed) and 52 males (3 neutered). Seven of the most recent 103 cases had two or more endocrine disorders, and 101 of the 108 cases where pedigrees were available showed a familial relationship going back several generations. Data from surveying the Bearded Collie breed reported 55 hypothyroid, 17 Addison's disease, and 31 polyglandular autoimmunity (5 were hypothyroid).

Aberrant Behavior and Thyroid Dysfunction

The principal reason for pet euthanasia stems not from disease, but undesirable behavior. While this abnormal behavior can have a variety of medical causes, it also can reflect underlying problems of a psychological nature.

An association between behavioral and psychologic changes and thyroid dysfunction has been recognized in humans since the 19th century. In a recent study, 66% of people with attention deficit-hyperactivity disorder were found to be hypothyroid, and supplementing their thyroid levels was largely curative. Furthermore, an association has recently been established between aberrant behavior and thyroid dysfunction in the dog, and has been noticed in cats with hyperthyroidism. Typical clinical signs include unprovoked aggression towards other animals and/or people, sudden onset of seizure disorder in adulthood, disorientation, moodiness, erratic temperament, periods of hyperactivity, hypoattentiveness, depression, fearfulness and phobias, anxiety, submissiveness, passivity, compulsiveness, and irritability. After episodes, most of the animals appeared to come out of a trance like state, and were unaware of their bizarre behavior.

The mechanism whereby diminished thyroid function affects behavior is unclear. Hypothyroid patients have reduced cortisol clearance, as well as suppressed TSH output and lowered production of thyroid hormones. Constantly elevated levels of circulating cortisol mimic the condition of an animal in a constant state of stress. In people and seemingly in dogs, mental function is impaired and the animal is likely to respond to stress in a stereotypical rather than

reasoned fashion. Chronic stress in humans has been implicated in the pathogenesis of affective disorders such as depression. Major depression has been shown in imaging studies to produce changes in neural activity or volume in areas of the brain which regulate aggressive and other behaviors. Dopamine and serotonin receptors have been clearly demonstrated to be involved in aggressive pathways in the CNS. Hypothyroid rats have increased turnover of serotonin and dopamine receptors, and an increased sensitivity to ambient neurotransmitter levels.

Investigators in recent years have noted the sudden onset of behavioral changes in dogs around the time of puberty or as young adults. Most of the dogs have been purebreds or crossbreeds, with an apparent predilection for certain breeds. For a significant proportion of these animals, neutering does not alter the symptoms and in some cases the behaviors intensify. The seasonal effects of allergies to inhalants and ectoparasites such as fleas and ticks, followed by the onset of skin and coat disorders including pyoderma, allergic dermatitis, alopecia, and intense itching, have also been linked to changes in behavior.

Many of these dogs belong to a certain group of breeds or dog families susceptible to a variety of immune problems and allergies (e.g. Golden Retriever, Akita, Rottweiler, Doberman Pinscher, English Springer Spaniel, Shetland Sheepdog, and German Shepherd Dog). The clinical signs in these animals, before they show the sudden onset of behavioral aggression, can include minor problems such as inattentiveness, fearfulness, seasonal allergies, skin and coat disorders, and intense itching. These may be early subtle signs of thyroid dysfunction, with no other typical signs of thyroid disease being manifested.

The typical history starts out with a quite, well-mannered and sweet-natured puppy or young adult dog. The animal was outgoing, attended training classes for obedience, working, or dog show events, and came from a reputable breeder whose kennel has had no prior history of producing animals with behavioral problems. At the onset of puberty or thereafter, however, sudden changes in personality are observed. Typical signs can be incessant whining, nervousness, schizoid behavior, fear in the presence of strangers, hyperventilating and undue sweating, disorientation, and failure to be attentive. These changes can progress to sudden unprovoked aggressiveness in unfamiliar situations with other animals, people and especially with children.

Another group of dogs show seizure or seizure-like disorders of sudden onset that can occur at any time from puberty to mid-life. These dogs appear perfectly healthy outwardly, have normal hair coats and energy, but suddenly seizure for no apparent reason. The seizures are often spaced several weeks to months apart, may coincide with the full moon, and can appear in brief clusters. In some cases the animals become aggressive and attack those around them shortly before or after having one of the seizures. Two recent cases involved young dogs referred for sudden onset seizure disorder shortly after puberty. Both dogs were found to have early onset autoimmune thyroiditis, which was clinically responsive to thyroid supplementation, to the extent that anticonvulsant medications could be gradually withdrawn. The numbers of animals showing these various types of aberrant behavior appear to be increasing in frequency over the last decade.

In dogs with aberrant aggression, a large collaborative study between our group and Dr. Dodman and colleagues at Tufts University School of Veterinary Medicine has shown a favorable response to thyroid replacement therapy within the first week of treatment, whereas it took about three weeks to correct their metabolic deficit. Dramatic reversal of behavior with resumption of

previous problems has occurred in some cases if only a single dose is missed. A similar pattern of aggression responsive to thyroid replacement has been reported in a horse.

Tables 1-2 summarize results of complete thyroid diagnostic profiling on 634 canine cases of aberrant behavior, compiled by this author in collaboration with Drs. Nicholas Dodman, Linda Aronson, and Jean DeNapoli of Tufts University School of Veterinary Medicine, North Grafton, MA. Ninety percent (568 dogs) were purebreds and 10% were mixed breeds. There was no sex predilection found in this case cohort, whether or not the animals were intact or neutered. Sixty-three percent of the dogs had thyroid dysfunction as judged by finding 3 or more abnormal results on the comprehensive thyroid profile. The major categories of aberrant behavior were aggression (40% of cases), seizures (30%), fearfulness (9%), and hyperactivity (7%); some dogs exhibited more than one of these behaviors (Table 2). Within these 4 categories, thyroid dysfunction was found in 62% of the aggressive dogs, 77% of seizuring dogs, 47% of fearful dogs, and 31% of hyperactive dogs.

Outcomes of treatment intervention with standard twice daily doses of thyroid replacement were evaluated in 95 cases, and showed a significant behavioral improvement in 61% of the dogs. Of these, 58 dogs had greater than 50% improvement in their behavior as judged by a predefined 6-point subjective scale (34 were improved > 75%), and another 23 dogs had >25 but <50% improvement. Only 10 dogs experienced no appreciable change, and 2 dogs had a worsening of their behavior. When compared to 20 cases of dominance aggression treated with conventional behavior or other habit modification over the same time period, only 11 dogs improved more than 25%, and of the remaining 9 cases, 3 failed to improve and 3 were euthanized or placed in another home. These initial results are so promising that complete thyroid diagnostic profiling and treatment with thyroid supplement, where indicated, is warranted for all cases presenting with aberrant behavior.

Our ongoing study now includes over 1500 cases of dogs presented to veterinary clinics for aberrant behavior. The first 499 cases have been analyzed independently by a neural network correlative statistical program. Results showed a significant relationship between thyroid dysfunction and seizure disorder, and thyroid dysfunction and dog-to-human aggression.

Collectively, these findings confirm the importance of including a complete thyroid antibody profile as part of the laboratory and clinical work up of any behavioral case.

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Table 1. CLINICAL SIGNS OF CANINE HYPOTHYROIDISM

Alterations in Cellular Metabolism	
lethargy	weight gain
mental dullness	cold intolerance
exercise intolerance	mood swings
neurologic signs	hyperexcitability
polyneuropathy	stunted growth
seizures	chronic infections
Neuromuscular Problems	
weakness	knuckling or dragging feet
stiffness	muscle wasting

Table 1 (cont'd)

laryngeal paralysis	megaesophagus
facial paralysis	head tilt
"tragic" expression	drooping eyelids
incontinence	ruptured cruciate ligament

Dermatologic Diseases

dry, scaly skin and dandruff	chronic offensive skin odor
coarse, dull coat	bilaterally symmetrical hair loss
"rat tail"; "puppy coat"	seborrhea with greasy skin
hyperpigmentation	seborrhea with dry skin
pyoderma or skin infections	myxedema

Reproductive Disorders

infertility	prolonged interestrus interval
lack of libido	absence of heat cycles
testicular atrophy	silent heats
hypospermia	pseudopregnancy
aspermia	weak, dying or stillborn pups

Cardiac Abnormalities

slow heart rate (bradycardia)
cardiac arrhythmias
cardiomyopathy

Gastrointestinal Disorders

constipation
diarrhea
vomiting

Hematologic Disorders

bleeding
bone marrow failure
low red blood cells (anemia), white blood cells, platelets

Ocular Diseases

corneal lipid deposits	corneal ulceration
uveitis	keratoconjunctivitis sicca or "dry eye"
infections of eyelid glands (Meibomian gland)	Vogt-Koyanagi-Harada syndrome

Other Associated Disorders

IgA deficiency	loss of smell (dysosmia)
loss of taste	glycosuria
other endocrinopathies	chronic active hepatitis
adrenal	
pancreatic	
parathyroid	

Table 2. DIAGNOSIS OF THYROID DISEASE

X Complete Basic Profile
-- (T4, T3, FT4, FT3, T4AA, T3AA)

X Additional Tests
-- (TSH, TgAA)

X Older Tests (T4, T4 + T3)

Serum T4 and/or T3 alone are **not** reliable for diagnosis because:

-- overdiagnose hypothyroidism
-- underdiagnose hyperthyroidism
-- fail to dectect early compensatory disease and thyroiditis
-- influenced by nonthyroidal illness and certain drugs

X Newer Tests

Free (Unbound) T4

Less likely to be influenced by nonthyroidal illness or drugs

Valid
-- equilibrium dialysis
-- solid-phase analog RIA
-- chemiluminescence solid-phase
Less reliable -- liquid-phase analog RIA

Endogenous Canine TSH

In primary hypothyroidism, as serum free T4 levels fall, pituitary output of TSH rises.

-- elevated TSH usually indicates primary thyroid disease
-- 20-40% discordancy observed between expected and actual findings
-- published normal ranges may need revising upwards
-- affected by concomitant chronic renal disease

Canine TgAA

Thyroglobulin autoantibodies are present in serum of cases with lymphocytic thyroiditis.

-- positive results confirm diagnosis
-- 20-40% of cases have circulating T3 and/or T4AA
-- allows for early diagnosis and genetic counselling

Table 3. CANINE ABERRANT BEHAVIOR *

Total No. Cases	Purebreds	Mixed Breeds	Thyroid Dysfunction	Euthyroid
634	568	66	401 †	233

* Mean Age, 3.7 years (Range 0.5-12 years). Median Age, 2.5 years.

Table 4. MOST COMMONLY REPRESENTED BREEDS WITH THYROID DYSFUNCTION AND ABERRANT BEHAVIOR *

Breed†	Thyroid Dysfunction 401/634 (63%)	Aggression 251/634 (40%)	Seizures 189/634 (30%)	Fearful 55/634 (9%)	Hyperactive 42/634 (7%)
Golden Retriever	50/73	12/16	22/30	4/6	1/6
German Shepherd	34/53	10/22	14/16	3/7	2/2
Akita	27/38	24/33	0/1	0	0/2
Labrador Retriever	8/30	6/11	12/16	2/15	0/3
Shetland Sheepdog	14/25	3/6	2/3	2/4	3/3
Collie	8/9	0	7/7	0	0
English Setter	4/6	1/1	0	1/3	1/2
Other Purebreds	217/334	89/135	72/93	10/15	5/16
Mixed Breed	39/66	11/27	16/23	4/5	1/8
Totals	401/634 (63%)	156/251 (62%)	145/189 (77%)	26/55 (47%)	13/42 (31%)

* Some dogs had more than 1 abnormal behavior. Numerator = Thyroid dysfunction Denominator = Aberrant behavior † Total 634 cases; 72 dogs breeds represented.